

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
31 July 2003 (31.07.2003)

PCT

(10) International Publication Number
WO 2003/062206 A3

(51) International Patent Classification⁷: **C07D 231/16**,
231/14, 231/12, 401/12, 409/04, A61K 31/415, 31/4155,
A61P 7/02, 9/10

(21) International Application Number:
PCT/US2003/002059

(22) International Filing Date: 23 January 2003 (23.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/386,198 23 January 2002 (23.01.2002) US
60/386,384 5 June 2002 (05.06.2002) US
60/401,467 5 August 2002 (05.08.2002) US

(71) Applicant (*for all designated States except US*): **ARENA PHARMACEUTICALS, INC.** [US/US]; 6166 Nancy Ridge Drive, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **TEEGARDEN, Bradley** [US/US]; 11933 Windom Peak Way, San Diego, CA 92131 (US). **DROUET, Keith** [US/US]; 10751 Juniper Park Lane, San Diego, CA 92121 (US). **JAYAKUMAR, Honnappa** [US/US]; 13323 Caminito Ciera, #107, San Diego, CA 92129 (US). **THOMSEN, William** [US/US]; 13603 Mar Scenic, Del Mar, CA 92014 (US). **MAFFUID, Paul** [US/US]; 3326 Avenida Anacapa, Carlsbad, CA 92009 (US). **ELWELL, Katie** [US/US]; 103 Guerrero Court, Solana Beach, CA 92075 (US). **FOSTER, Richard** [GB/GB]; Puffins Cottage, Poundstock Bude, Cornwall EX23 0AX (GB). **LAWLESS, Michael** [US/US]; 1847 Willow Oak Drive, St. Charles, MO 63303 (US). **LIU,**

Qian [US/US]; 310 Shady Meadows Drive, Ballwin, MO 63011 (US). **SMITH, Julian** [GB/GB]; 2 Exeview Cottages, Whitestone, Exeter, Devon EX4 2JJ (GB). **FEICHTINGER, Konrad** [DE/US]; 3533 6th Avenue, #3, San Diego, CA 92103 (US).

(74) Agents: **BRADFUTE, David** et al.; Arena Pharmaceuticals, Inc., 6166 Nancy Ridge Drive, San Diego, CA 92121 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
8 January 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SMALL MOLECULE MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR USEFUL FOR THE PROPHYLAXIS AND TREATMENT OF DISORDERS RELATED THERETO

(57) Abstract: The present invention relates to certain pyrazole derivatives of Formula (I) and pharmaceutical compositions thereof that modulate the activity of the 5-HT_{2A} serotonin receptor. Formula (I): Compounds and pharmaceutical compositions thereof are directed to methods useful in the prophylaxis or treatment of reducing platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia and related disorders. The present invention also relates to the method of prophylaxis or treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with a dopamine D2 receptor antagonist such as haloperidol, administered separately or together.



WO 2003/062206 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/02059

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/16 C07D231/14 C07D231/12 C07D401/12 C07D409/04
A61K31/415 A61K31/4155 A61P7/02 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 52927 A (SMITH JULIAN R; FOSTER RICHARD J (GB); ARENA PHARMACEUTICALS INC) 21 October 1999 (1999-10-21) page 31, line 8 -page 37, line 9 page 39 -page 45 page 47 -page 49, line 4 page 51 -page 54 claims 14-20	1-166
A	WO 98 24785 A (KATO MASAYUKI; NODA YUKA (JP); SPEARS GLEN W (JP); HARADA KEIKO (J) 11 June 1998 (1998-06-11) claims 1,2,5-8; examples	1,45,88, 129-166
A	US 5 281 571 A (MISCHKE DEBORAH A ET AL) 25 January 1994 (1994-01-25) claims 1-3	1,45,88
	--- -/-- ---	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

2 October 2003

Date of mailing of the international search report

10/10/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/02059

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>WO 02 076464 A (ARENA PHARMACEUTICALS INC; MENZAGHI FREDERIQUE (US); BEHAN DOMINIC) 3 October 2002 (2002-10-03)</p> <p>claims</p> <p>-----</p>	<p>1-3,7,8, 16-21, 24-30, 33, 45-47, 51,52, 60-65, 68-74, 77,129, 130, 132-166</p>

INTERNATIONAL SEARCH REPORT

international application No.
PCT/US 03/02059

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 129-131, 133-154 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/02059

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9952927	A	21-10-1999	AU 764766 B2	28-08-2003
			AU 3746699 A	01-11-1999
			CA 2325559 A1	21-10-1999
			DE 1071701 T1	23-08-2001
			EP 1071701 A1	31-01-2001
			ES 2156845 T1	01-08-2001
			JP 2003514763 T	22-04-2003
			US 2003023069 A1	30-01-2003
			WO 9952927 A1	21-10-1999
			US 6555339 B1	29-04-2003
			US 2003153004 A1	14-08-2003
			US 6107324 A	22-08-2000
			US 6541209 B1	01-04-2003
			US 6426541 B1	16-07-2002
			US 6420541 B1	16-07-2002
			US 2003105292 A1	05-06-2003
			US 6140509 A	31-10-2000
			US 6150393 A	21-11-2000
WO 9824785	A	11-06-1998	AU 5068298 A	29-06-1998
			WO 9824785 A1	11-06-1998
			JP 2001508767 T	03-07-2001
US 5281571	A	25-01-1994	AT 174330 T	15-12-1998
			AU 653758 B2	13-10-1994
			AU 8927591 A	20-05-1992
			BG 97638 A	31-03-1994
			BR 9107049 A	28-09-1993
			CA 2092083 A1	19-04-1992
			CN 1061777 A , B	10-06-1992
			CN 1090845 A , B	17-08-1994
			CZ 9300637 A3	15-12-1993
			DE 69130614 D1	21-01-1999
			DE 69130614 T2	08-07-1999
			DK 553307 T3	16-08-1999
			EP 0553307 A1	04-08-1993
			EP 0791571 A1	27-08-1997
			ES 2059290 T1	16-11-1994
			FI 931708 A	10-06-1993
			GR 3029621 T3	30-06-1999
			HU 64310 A2	28-12-1993
			HU 219574 B	28-05-2001
			IE 913642 A1	22-04-1992
			IE 990098 A1	01-11-2000
			JP 6502637 T	24-03-1994
			MX 9101637 A1	05-06-1992
			NZ 240282 A	27-04-1994
			PT 99261 A , B	31-08-1992
			RU 2137761 C1	20-09-1999
			SK 35993 A3	07-07-1993
			WO 9206962 A1	30-04-1992
			US 5489571 A	06-02-1996
			US 5536700 A	16-07-1996
			US 5530126 A	25-06-1996
			US 5600008 A	04-02-1997
			US 5600016 A	04-02-1997
			US 5496956 A	05-03-1996
			US 5866723 A	02-02-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

ational Application No

PCT/US 03/02059

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5281571	A	PL 168964 B1	31-05-1996
		PL 170158 B1	31-10-1996
		PL 169882 B1	30-09-1996
		ZA 9108291 A	26-08-1992
WO 02076464	A	03-10-2002	WO 02076464 A1
			US 2002156068 A1
			24-10-2002